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Anaphylactic Deaths: A Clinicopathologic Study of 43 Cases

The concept of anaphylaxis originates from the observations by the French physiologist Charles Richet in 1902 of the effects of actinotoxins on the blood pressure of dogs [*1*]. Anaphylactic shock is the classic example of the immediate type of hypersensitivity reaction; it may be defined as the failure of the peripheral circulation induced by an antigen-antibody reaction [*2*]. The circulatory collapse may be primary, if the circulatory reaction is the primary event, or secondary, if the circulatory collapse is the consequence of an initial respiratory insufficiency.

The immune mechanisms of anaphylaxis have been extensively investigated in recent years [*3–5*]. Injection in an already sensitized animal of a foreign (antigenic) substance induces an antigen-antibody reaction that may either cause damage at the site of union to a number of cells or trigger the release into the circulation of powerful pharmacologically active agents or their activators, which will in turn react at secondary sites (usually smooth muscle and vascular tissue of selective "shock organs") to produce the dramatic acute systemic clinical manifestations. The pharmacologic mediators found in man and animals are [*6*]:

1. Vasoactive amines: histamine, serotonine;
2. Vasoactive peptides: the kinins, of which bradikinin is the best known;
3. Large molecular substances: slow-reacting substances of anaphylaxis (SRS-A), anaphylactoxin; and
4. Autonomic nervous system mediators: catecholamines, acetylcholine.

These mediators are responsible for the reactions such as contraction of smooth muscle (bronchospasm), vasodilatation, and increased capillary permeability observed in anaphylactic shock. The shock organs vary with the species, and the clinical picture depends upon the tissues involved ("shock tissue") [*7*]. Probable shock organs in different animal species that have been reported are (a) in the guinea pig: the pulmonary apparatus, with death resulting from asphyxia secondary to severe bronchospasm caused by contraction of the bronchial smooth musculature; (b) in the rabbit: the pulmonary arterial tree, with death the consequence of circulatory failure resulting from the obstruction of the pulmonary circulation; (c) in the dog: the liver, death being produced by circulatory collapse

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caused by obstruction in the portal or splanchnic circulation from venospasm or both; (d) in the cat: the lung, death being from acute pulmonary emphysema [8]; (e) in the rat: the intestinal mass, death resulting from a circulatory failure in the splanchnic area [9]; (f) in the mouse: fatal anaphylaxis from insufficient oxygenation of the tissues resulting from severe loss of blood volume because of dilation of the capillary bed [10].

No specific pattern of anaphylaxis has been outlined in man. Human anaphylaxis can resemble that of several animal species, in particular the guinea pig, the rabbit, or the dog [11]. Edema of the upper respiratory tract in some cases of human anaphylactic fatalities seems to represent a unique feature [12].

The phenomenon of anaphylaxis has always attracted considerable interest from the medical profession, and many case reports of anaphylactic shock have been reported in the literature following the administration of drugs [13–18], foreign sera [19,20], diagnostic agents [21–26], foods [27], exposure to pollens, and venoms from stinging insects [28,29] and snakes [30].

On the other hand, little information from autopsies on human victims dying of anaphylactic shock is available. Since Lamson's [31] report in 1929 of fatal anaphylactic shock in a patient following an injection of a desensitizing agent, in which the main finding at autopsy was "that the lungs were distended and did not collapse when the thoracic cavity was opened," scattered reports of isolated cases of anaphylactic deaths with often incomplete morphologic data have appeared in the medical literature over the subsequent years. The chief pathologic findings in such cases are: laryngeal edema [32–34], pulmonary emphysema [35–37], visceral congestion [38], pulmonary congestion associated with hemorrhage or edema or both [39], any combination of the above [40], or simply no significant morphologic findings at all [41,42]. James and Austen [43] in 1964 presented six well-documented cases with detailed autopsy data. In their series, five of the six cases showed the predominant changes to be in the respiratory system: four had obstructive edema of the upper respiratory tract; three showed acute pulmonary emphysema resulting from obstruction in the lower respiratory tree: and the sixth case differed from the others in that there was no respiratory involvement and death was caused by primary cardiovascular collapse.

The purpose of this paper is to present the clinicopathologic findings in 43 validated cases of drug-induced fatal anaphylactic shock.

Material and Methods

Forty-three validated cases of fatal anaphylactic reaction to a particular drug or diagnostic agent were taken from the files of the Armed Forces Institute of Pathology. Most of these cases were accessioned during the last decade and a half. In all, the clinical history of the present event was satisfactory, although in many cases little information was obtained in the past medical history as to previous exposures or reactions to a given allergenic agent and as to the existence of an underlying allergic condition (bronchial asthma, hay fever, various allergies, etc.). Complete autopsy protocols with hematoxylin and eosin (H&E) slides were available in all but three cases. Each individual chart was carefully reviewed, and all the available clinical data were abstracted. In the 40 cases in which autopsy material was available, slides of all organs were studied and the significant morphologic findings noted. Alterations in the respiratory tree were given a more detailed analysis and a tentative quantitative appreciation: according to their slight, moderate, or marked degree, these lesions were graded +, ++, or +++. Examination of the pathologic findings and their grading were done by the same pathologist.

Results

Our findings, clinical and pathologic, on the 43 validated cases of probable anaphylactic death appear in consolidated form in Table 1.

TABLE 1—*Clinicopathologic data on 43 cases of anaphylactic deaths.*

Patient Number	Age, years	Sex	Race	Therapeutic Indication	Agent	Dose	Route
1	40	M	C	Prostate hyperplasia	Meglumine diatrizoate	25 cc (15 g)	IV
2	36	F	C	Leukocytosis	Penicillin	600 000 UI	IM
3	49	M	C	Pharyngitis	Penicillin	600 000 UI	IM
4	42	F	C	Bronchitis	Penicillin	800 000 UI	Per os
5	38	M	C	Pheochromocytoma	BSP	?	IV
6	46	M	N	Gonorrhea	Penicillin	2 400 000 UI	IM
7	77	M	C	Prostate ca	Sodium diatrizoate	25 cc	IV
8	35	M	C	Peptic ulcer	BSP	"Recommended"	IV
9	18	M	C	Prophylaxis	Vaccine	?	IM and subcutaneous
10	40	M	C	Bronchoscopy	Hexylcaine 5%	?	Topical
11	23	M	N	Gonorrhea	Penicillin	?	IM
12	38	M	C	Coryza	Penicillin	?	"Injection"
13	43	M	C	Sinusitis	Penicillin	300 000 UI	IM
14	57	M	C	Minor surgery	Penicillin	?	IM
15	38	M	C	Coryza	Penicillin	300 000 UI	"Injection"
16	36	F	C	Asthma	Penicillin	300 000 UI	IM
17	33	M	C	Gonorrhea	Penicillin	300 000 UI	IM
18	28	M	C	Shell wound	Penicillin	100 000 UI in 1000 cc 5% glucose and saline	IV
19	28	M	C	Minor surgery	Penicillin	300 000 UI	"Injection"
20	32	F	C	Vaginitis	Penicillin	600 000 UI	IM
21	23	M	N	Gonorrhea	Penicillin	"1 cc"	IM
22	30	M	C	Finger laceration	Penicillin	600 000 UI	IM
23	42	M	C	TB	Penicillin	300 000 UI	IM
24	33	F	N	Pharyngitis	Penicillin	600 000 UI	"Injection"
25	23	F	C	Conjunctivitis	Penicillin	?	IM
26	48	M	N	Gonorrhea	Penicillin	300 000 UI	IM
27	4 mo	F	N	URI	Penicillin	300 000 UI	IM
28	50	M	C	Pharyngitis	Penicillin	?	"Injection"
29	53	F	C	Coryza	Penicillin	One tablet	Per o
30	7	F	A	Abdominal pain	Acetrizoate sodium	15 cc	IV
31	27	M	C	Gonorrhea	Penicillin	?	IM
32	1	M	C	Tonsillitis	Penicillin	?	"Injection"
33	8 mo	F	C	URI	Penicillin	600 000 UI	"Injection"
34	65	M	C	Pneumonitis	Penicillin	1 400 000 UI	IM
35	26	M	C	Urethral stricture	Tetracaine 4%	?	Intraurethral
36	31	M	C	Tonsillitis	Penicillin	600 000 UI	IM
37	62	M	C	Urethral stricture	Tetracaine 2%	?	Intraurethral
38	25	M	N	Gonorrhea	Penicillin	600 000 UI	IM
39	38	M	C	Teeth extraction	Penicillin	?	IM
40	45	F	C	UTI	Polymyxin B	100 mgm	IM
41	25	M	N	Gonorrhea	Penicillin	600 000 UI	IM
42	35	M	N	Asthma	Desensitizing agent (ragweed)	?	?
43	62	F	C	Pharyngitis	Penicillin	?	IM

Clinical Findings

Most of the patients (76 percent) were Caucasians, and there were more male than female victims (31/12). With the exclusion of four patients in the pediatric age group, the mean adult age was 39 years, the youngest patient being 18, the oldest 77.[2] Most of the

[2] The statistical data regarding race, sex, and age distribution must be appreciated in the context of the population being analyzed. Of the 43 patients, 28 were in the armed forces, while 15 were civilians. These demographic statistics therefore, should not be extrapolated and applied to the general population of the United States.

TABLE 2—*Previous exposure to the drug or agent.*

History of Exposure	Number of Cases	Percent of Cases
Presence of previous exposure	43	100
Yes	27	63
No	3	7
Not stated	13	30
Previous reaction	43	100
Yes	4	9
No	15	35
Not stated	24	56
History of allergy or atopy	43	100
Yes	7	16
No	10	23
Not stated	26	61

cases occurred between the third and fifth decades, with a peak in the fourth decade. In 19 patients the therapeutic accident happened while they were hospitalized, whereas in the majority it occurred while they were being treated in emergency or outpatient clinics for minor disorders.

In 32 patients (74 percent) the "basic disease" for which they received the allergenic drug or agent was an infection of either the upper respiratory or the urinary tract. The 11 other patients (26 percent) consulted for miscellaneous conditions, as shown in Table 1.

The purpose of the exposure to the responsible agent was therapeutic in 35 patients (81 percent), diagnostic in 6, and prophylactic in 2.

According to the available clinical data, 63 percent of the patients (Table 2) had previously been exposed to the offending drug (or agent), but only 9 percent had a precise history of previous reaction to the particular drug (or agent). In only 16 percent was there any indication in the clinical summary of a pre-existing hypersensitivity such as bronchial asthma, hay fever, or atopic dermatitis. These figures may be unduly low, however, because of incomplete information. For instance, in 30 percent of the cases, no information on previous exposure to the allegedly responsible drug was available; in 56 percent there were no data on previous reactions to the drug; and in 61 percent no statement was made as to any pre-existing hypersensitivity state.

Antibiotics comprised the most frequent category of agents involved (33 cases), followed by diagnostic agents (5 cases), local anesthetics (3 cases), and immunologic agents (2 cases).

Penicillin alone was responsible for nearly three out of four anaphylactic reactions. A host of various agents was incriminated in the remainder (Table 1).

In 36 cases (84 percent) the allergenic agent was administered by injection. In the other 7 (16 percent) the route was per os (2), intraurethral (2), subcutaneous (1), or topical (1), and in one case no such information was provided.

The most frequent initial features of patients undergoing anaphylactic shock were described as either acute respiratory distress or circulatory collapse (Table 3). Seizures, cyanosis, and gastrointestinal symptoms were in some instances the initial findings. In the majority of cases, two or more of the aforementioned findings were present in various combinations, although in a few cases a single one was the sole manifestation of anaphylaxis. For example, a patient would have acute respiratory distress accompanied almost simultaneously (in a matter of seconds) by cyanosis, cardiovascular failure, and seizures.

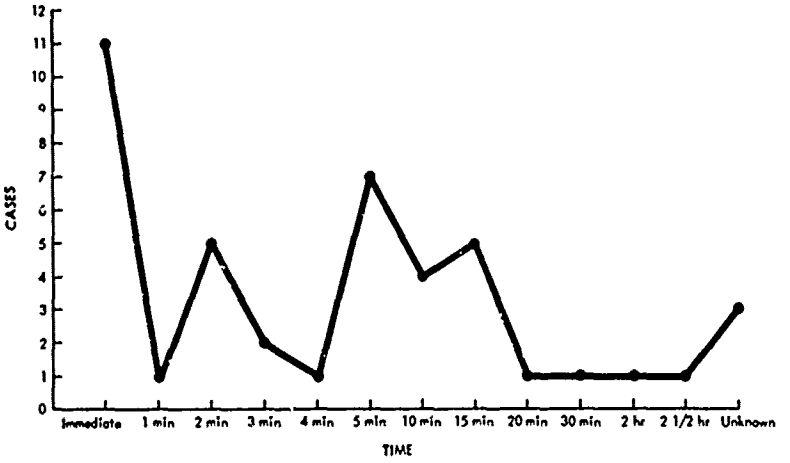

FIG. 1—*Interval between exposure and reaction to the agent in 43 cases of anaphylactic death.*

Figure 1 illustrates the characteristic short interval between exposure, and reaction to a particular allergenic agent; in 37 cases (86 percent) the onset of anaphylaxis occurred within the first 20 minutes; one patient went into (delayed) anaphylactic shock in less than 2 hours following the administration of 600,000 units of penicillin (exact route not stated); in another, who had been given 100,000 units of penicillin intravenously in 1000 cc of 5 percent glucose and saline, the interval to symptoms was about 2½ hours. No time-related data were provided in three cases.

The period from the onset of anaphylaxis to death varied considerably, depending upon the availability of equipment and the efficacy of the emergency measures taken. Most of the patients expired within five hours (Fig. 2).

Pathologic Findings

Pathologic findings were nonspecific (Table 4) and consisted of mild to severe pulmonary congestion, sometimes associated with variable edema (Fig. 3) or intra-alveolar

TABLE 3—*Initial symptoms and signs in 43 cases of anaphylactic deaths.*

Initial Symptoms and Signs	Number of Cases
Respiratory distress	16
Circulatory collapse	14
Seizures	11
Cyanosis	11
Nausea and vomiting	10
Dizziness and weakness	6
Skin eruptions	3
Numbness and tingling sensations	3
Swelling of face	1
Sudden deaths with unknown symptoms	4

TABLE 4—*Pathologic findings in 40 cases of unaphylactic deaths.*

Pathologic Finding	Number of Cases
Pulmonary congestion	36
Pulmonary edema	20
Intra-alveolar hemorrhage	18
Tracheobronchial secretions	18
slight	5
moderate	9
marked	4
Laryngeal edema	15
slight	5
moderate	6
marked	4
Pulmonary emphysema (acute)	11
diffuse	4
focal	7
Splenic eosinophils	9

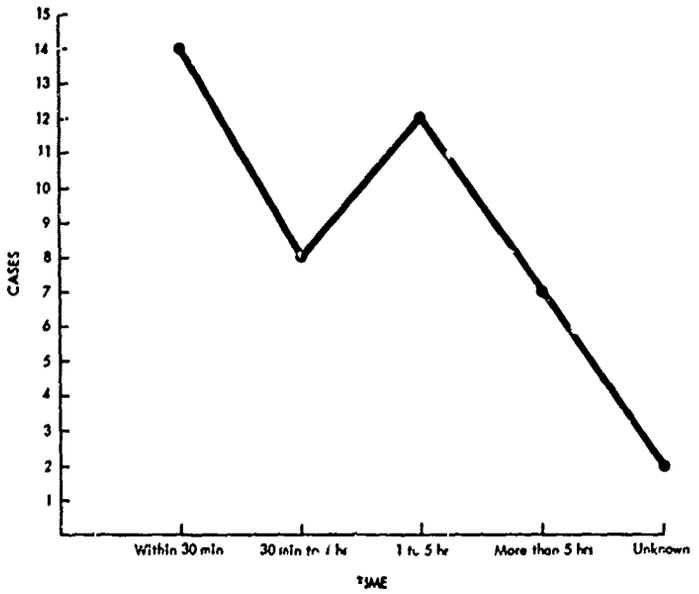

FIG. 2—*Interval between exposure to the agent and death in 43 cases of fatal anaphylaxis.*

hemorrhage (Fig. 4), or both. Increased tracheobronchial secretion of mucus was present in 18 patients, but in only 4 was this hypersecretion of a severe degree.

Interestingly, 15 patients had some degree of laryngeal edema, but in only 4 was it so marked as to completely obstruct the upper airways and be considered as the primary cause of death. Grading of laryngeal (and upper respiratory tract) edema ranged from slight to marked. The term "slight" was used when there was only microscopic evidence of edematous fluid in the lamina propria of the mucosa, without distortion of the laryngeal structures; "moderate" when there was gross evidence of swelling of the laryngeal structures (Fig. 5), with obliteration or narrowing of the venticular folds but without obstruction of the air passages; "marked" when considerable swelling and distortion of the laryngeal structures were present (Fig. 6), with complete obstruction of the upper respiratory airways.

Pulmonary emphysema was seen in 11 patients (acute obstructive type): in 4 the process was diffuse in both lungs, and in 2 of these the hyperdistension of the lungs was very marked (Fig. 7), while in the other 7 patients, foci of hyperdistension alternated with areas of collapse (Fig. 8). The lungs were generally heavy, and their combined weight averaged 1200 g in the adult patients.

An increased number of eosinophils was noted in the red pulp of the spleen of nine patients. Numbers of eosinophils per high-power field (×1090) in these nine patients were as follows: 11.5, 5.7, 3.0, 2.2, 2.1, 1.8, 1.7, 1.3, and 1.2, respectively. No significant increase in eosinophils was observed in other organs, except in the lungs in one case—that of an asthmatic patient who had the characteristic bronchial changes associated with this condition.

Comment

The understanding of the penicillin allergy system has contributed immensely to a better knowledge of the immune mechanisms of drug allergy in general [*44,45*]. According

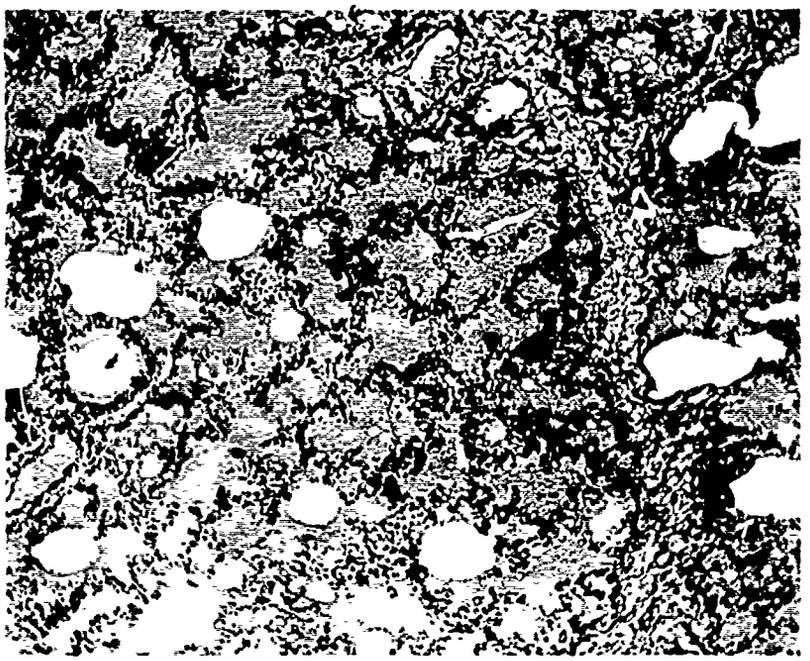

FIG. 3—*Pulmonary septa are thickened and congested, and alveoli are filled with edamatous fluid (hematoxylin and eosin, ×100; AFIP Neg. 71-1857).*

to Levine [*46,47*] an allergic drug reaction may be considered as emulating from a series of three kinds of molecular events: (1) the reaction of the drug (or metabolites, or degradation products of the drug) with tissue proteins, forming hapten-protein conjugates; (2) the induction of the hapten-protein conjugates of antibody synthesis (specific for the drug-derived haptens); (3) the interaction of antibody plus antigen in tissue, producing allergic tissue damage. A good body of evidence suggests that the serum of penicillin allergics contains skin-sensitizing antibodies with independent specificity for three antigens: benzylpenicillin, the penicilloyl radical, and benzylpenicilloate [*48*]. Anaphylactic reactions to penicillin are mediated by the reaginic antibodies (Ig E).

Penicillin is by far the most frequently involved agent in drug allergy [*49,50*]. Since Waldbiott [*51*] reported the first anaphylactic death from penicillin in 1949, a sizable number of similar cases were added over the years [*52,53*]. Precise data on the incidence of anaphylactic reactions to penicillin are difficult to obtain, and they vary according to different sources. It is estimated that such reactions occur in about 1 to 5 per 10,000 patient courses of penicillin [*54*]. According to a World Health Organization (WHO) survey [*55*], anaphylactic reactions may occur in about 0.015 to 0.004 percent, with a fatality rate from shock of 0.0015 to 0.002 percent, of treated patients. This WHO investigation included a

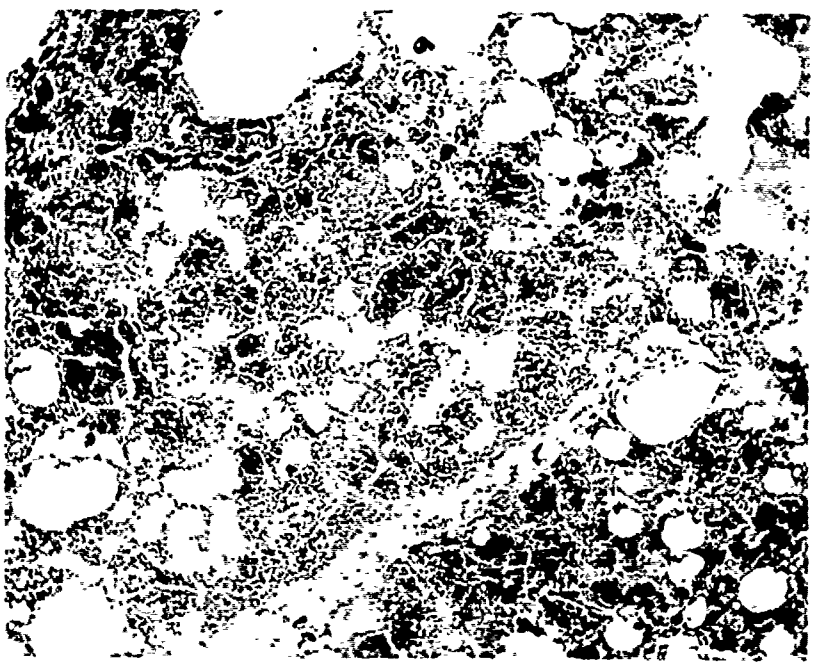

FIG. 4—*Pulmonary congestion with edema and marked intra-alveolar hemorrhage (hematoxylin and eosin, ×50; AFIP Neg. 71-1910).*

study of 151 anaphylactic fatalities (with no autopsy data, however) following penicillin administration, based on available medical literature during the period 1951–1965. Of this group, 28 percent had previous histories of allergies of some kind. 69 percent had received penicillin in the past, and 36.5 percent of the latter (38 of 104 patients) had experienced sudden allergic reactions in the past. In comparison, in our series of 32 cases of penicillin-induced anaphylaxis, 19 percent had evidence of some previous allergic experience such as urticaria, hay fever, or asthma; 69 percent had been exposed to penicillin at some time in their lives and 22.7 percent of the latter (5 of 22) acknowledged a previous reaction to penicillin. Although our series was much smaller, the data compare with those of the large WHO study. In both series, however, the statistical value of the tabulated data is limited by the rather high percentage of unknown or uncertain information given.

Not infrequently a patient is unaware of a previous exposure and will deny having received penicillin in the past [56]. He may also have had well-tolerated doses. In addition, the following comment by Fishman and Hewitt [45] is appropriate: "The usage of penicillins has been so widespread that a strong likelihood exists that everyone has had exposure to them in one form or another even without receiving penicillin therapeutically. Potential sources for contact include foods and milk from animals treated with penicillins, and vaccines to which penicillin is added to suppress bacterial contamination."

One of the most important clinical factors in anaphylaxis is the characteristically short interval between exposure and reaction to a given allergenic drug. According to Hoigné [2] the reaction times may be classified as follows: 0 to 1 hour—acute allergic reactions (almost all cases of anaphylactic shock); 1 to 24 hours—subacute allergic reactions (mostly exanthemas and drug fever); 1 day to several weeks—latent type of allergic reactions

FIG. —*Low-power view of laryngeal structures showing moderate edema of lamina propria. Ventricle of Morgani is narrowed by the swollen mucosa (hematoxylin and eosin, ×10; AFIP No. 71-1918).*

(serum sickness). Levine [*44*] proposed a somewhat different classification of allergic reactions after his studies of the immune mechanisms of penicillin allergy, the reactions may be immediate– 2 to 20 min after contact with the drug (urticaria, hypotension, shock, and when the reaction is severe, anaphylaxis); accelerated—2 to 28 hours (urticaria, occasionally laryngeal edema); late—more than 3 days (rashes, drug fever, hemolytic anemia).

In most of the 151 fatal cases compiled in the WHO study [*55*], the symptoms leading to death occurred within 15 minutes. This is in accordance with the figures in our series, in which the onset of anaphylaxis occurred within the first 20 minutes following contact with the allergenic agent in almost 90 percent of the patients. Recognition by the physician of early clinical manifestations of anaphylaxis may prove of paramount importance, for if these very first symptoms are recognized the physician may gain valuable time in treating such a critical emergency. Some patients undergoing anaphylaxis have symptoms of itching of the skin, flushing, generalized warmth, evidence of contraction of smooth muscle of the gastrointestinal tract, genitourinary tract, and uterus before they develop the full-blown characteristic symptomatology of anaphylaxis, such as life-threatening obstruc-

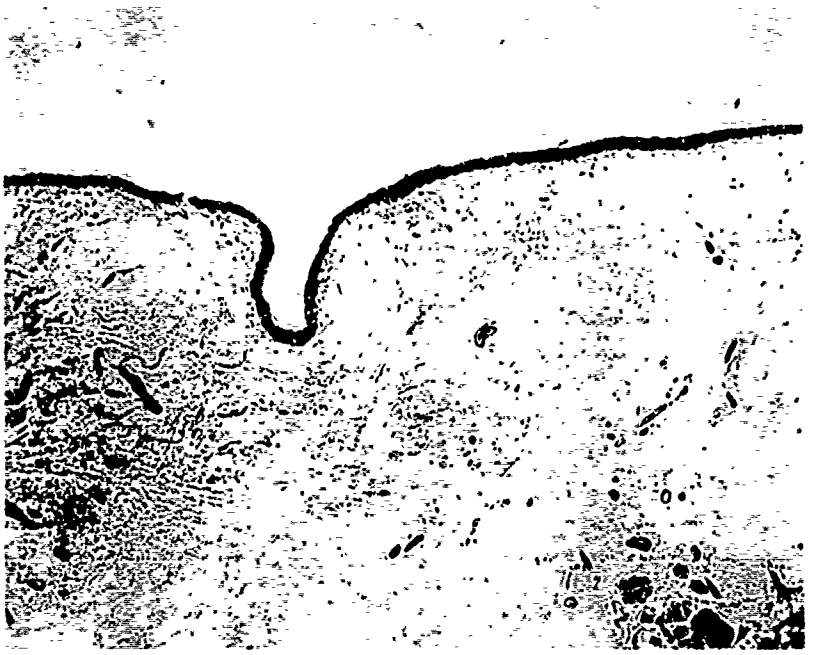

FIG. 6—*Marked laryngeal edema. Lamina propria and underlying structures disrupted by abundant edematous fluid, with almost total obliteration of ventricle of Morgani (hematoxylin and eosin,* ×8; *AFIP Neg. 71-1906).*

tion of the airway or vascular collapse. Unfortunately, owing to the rapidity of the event and the dramatic circumstances involved, these initial manifestations of anaphylaxis often go unnoticed or are not recorded, and many of these patients do not come to medical attention until they exhibit the full-blown picture of anaphylactic shock. The above factors may account for the small number of these early symptoms we were able to abstract from the charts analyzed in our series, which are listed in Table 3. In most instances in our 43 cases, the narrative summaries contained a description of the more obvious symptoms and signs of the fully developed anaphylactic shock as observed by relatives or people in the entourage of the patients at the moment of the incident.

In contrast to James' and Austen's [*43*] finding of acute pulmonary emphysema in half of their 6 patients dead of anaphylaxis, such a change was observed in only 11 of the 40 cases in our series on whom there was satisfactory autopsy information. Although obstructive laryngeal edema seems related only to human anaphylaxis, this feature was rather the exception than the rule in our cases, for it was present in about only one out of four patients. Complete obstruction of the airways was seen in but four patients. The most common finding was nonspecific congestion of the lungs with variable degrees of edema and hemorrhage. Pulmonary congestion was invariably found to some extent except in the four cases in which acute diffuse emphysema had completely distended the parenchyma of the lung. Notwithstanding the fact that congestion, edema, and intra-alveolar hemorrhage are not specific to anaphylaxis, these nevertheless were the most frequent pathologic findings in our 40 cases that had adequate autopsy material. It may be argued that these pulmonary changes may be related to some resuscitating maneuvers or to a prolonged

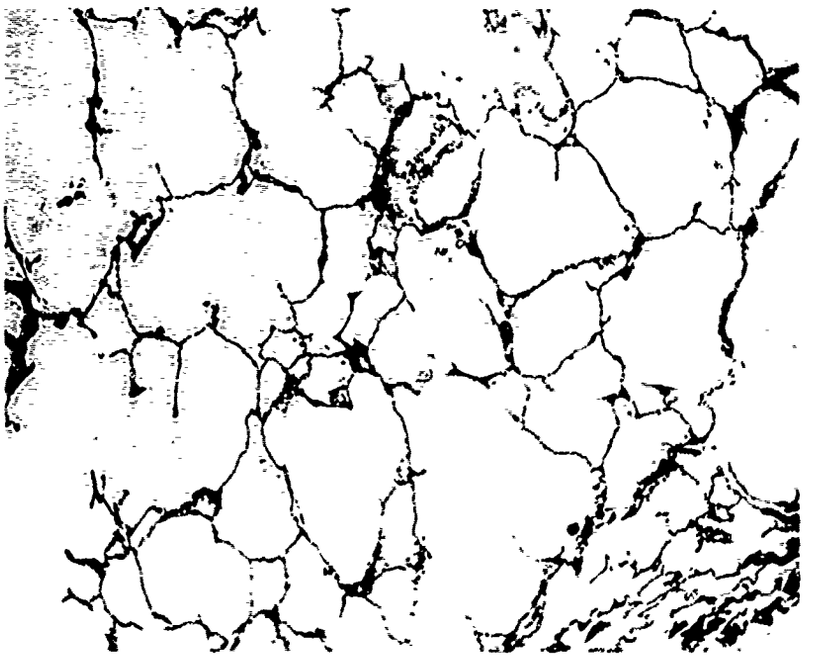

FIG. 7—*Acute hyperdistension of pulmonary alveoli with marked thinning of septa (obstructive emphysema) (hematoxylin and eosin, ×55; AFIP Neg. 71-2749).*

agonal state in the presence of inadequate oxygenation. Although these factors may have played a role in those cases in which resuscitating maneuvers provided a rather long survival period following onset of anaphylaxis, they could not, on the other hand, be blamed in those cases in which the same histologic alterations were found in the lungs in spite of death occurring a very short time after onset of the incident. For instance, in the nine cases (see Table 1, case numbers 3, 5, 14, 15, 16, 27, 33, 34, and 38) of our series in which death occurred within ten minutes following anaphylactic shock, there was some degree of pulmonary congestion in all, moderate to marked edema in four, and slight to moderate intra-alveolar hemorrhage in four.

There is no morphologic indication that these findings can be directly related to the mechanism of anaphylaxis per se, for they are common in other types of shock and may be explained on the basis of the anoxia resulting from primary cardiovascular collapse or acute respiratory depression. Regardless of their pathophysiology, however, and although they are not as suggestive of anaphylaxis as acute pulmonary emphysema and obstructive laryngeal edema, congestion alone or associated with edema and hemorrhage in the lungs may be the only significant pathologic findings one may see in fatal anaphylaxis.

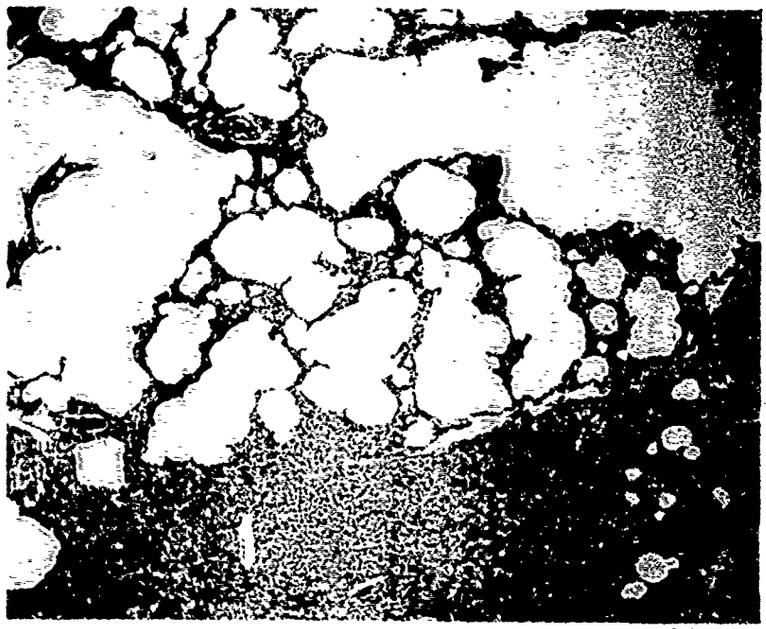

FIG. 8—*Top—section of the lung showing focal alveolar hyperdistension. Bottom—area of atelectasis (hematoxylin and eosin, ×42; AFIP Neg. 71-2747).*

There have been quite a few reports of myocardial damage during anaphylaxis in the guinea pig [*57*], the dog [*58*], and the monkey [*59*], as well as electrocardiographic (EKG) evidence of myocardial involvement in man [*60,61*]. These EKG abnormalities are variable and include flattening and inversion of the T waves, elevation and depression of the ST segment, nodal rhythm, and atrial fibrillation [*62*]. Hanashiro and Weil [*63*] analyzed hemodynamic and metabolic defects of anaphylactic shock in two patients. Their findings were that shock was due to a critical reduction in plasma volume and that in both cases there was evidence of acute myocardial injury, indicated by acute changes in ST and T waves. No histologic evidence of acute myocardial lesions was seen in the standard H&E stains in our series. This is understandable, since it is not possible to detect any definite histologic changes by routine light microscopy for the first five or six hours after the onset of myocardial ischemia [*64*].

Studies have shown indication of embolism in the microcirculation of several experimental animals. Amorphous hyaline [*65,66*] or fibrinoid [*67*] material has been observed in anaphylaxis in sections of the lungs of rabbits stained by H&E or in lung tissue of guinea pigs prepared for electron microscopy [*68*]. Robb [*69*] demonstrated platelet microemboli by cinematography as they lodged in the lungs of rabbits, blocking the circulation. He suggests that such platelet emboli occur also in man but that their recognition in postmortem sections is most difficult because of the fact that they are no longer in movement. Intravascular occlusions in the guinea pig have been denied by others [*70*].

A study of all lung tissue sections in our human series failed to reveal convincing evidence of microembolism.

The liver seems to be rarely affected in human anaphylaxis. Murphy and Mireles [71] reported a case of eosinophilic (hyaline) midzonal liver necrosis in a 66-year-old woman who went into anaphylactic shock after an injection of penicillin. Death occurred 50 hours later. To our knowledge, such a lesion has never been reported elsewhere, either in man or in animals, and none of our cases exhibited similar hepatocellular damage.

In two of the cases of anaphylactic deaths published by James and Austen [43], increased numbers of eosinophils were observed in the sinusoids of the spleen and liver as well as in the lamina propria of the upper respiratory tract and the pulmonary capillaries. Increased eosinophilia in tissues in human anaphylaxis has also been reported elsewhere [72,73].

A preliminary screening for splenic eosinophils was done in each of the 43 cases in our series. Of these nine who showed an apparent increase in the number of eosinophils were submitted to a quantitative evaluation. The eosinophils in 50 oil-immersion (×1000) fields in the red pulp of the spleen of these patients were counted. The figures established by James and Austen in ten consecutive unselected autopsies were used as normal base-line controls: 0 to 1.0 eosinophil in the spleen per high-power field. In all our cases the number of eosinophils exceeded those of the controls. This finding of more eosinophils than usual in the spleen was not significantly paralleled in any other organ. In the lungs or the lamina propria of the upper respiratory tract, for instance, the number of eosinophils was not above that of the normal population for these regions. The highest count, 11.5, was obtained in a 40-year-old man with sarcoidosis involving the lungs, the lymph nodes, and the spleen who also had a secondary opportunistic fungal (aspergillosis) pulmonary infection. That the high splenic eosinophilia in this case may be related to anaphylaxis following the application of topical anesthesia (hexylcaine) to the pharynx prior to a bronchoscopy is unlikely. Eosinophils most probably were present in the spleen in great numbers prior to this anaphylactic episode either as the result of sarcoidosis or previous sensitization (since the patient had a history of allergic rhinitis). It is interesting that six of the other eight patients had a previous exposure or reaction or both to the allergenic drug, suggesting that the presence of eosinophils in the spleen may be related to previous sensitization more likely than being the direct consequence of anaphylaxis. Moreover, the rapidity with which the anaphylactic response takes place makes the idea of so many eosinophils reaching the spleen in such a short time quite improbable. Since a postulated function of eosinophils is phagocytosis of antigen-antibody complexes [74,75], there is a likelihood that the eosinophils in the spleen had been there for some time and represent evidence of previous sensitization.

Conclusions

The present study has enumerated the clinical and pathologic features in 43 anaphylactic deaths. A diagnosis of anaphylaxis cannot be made on morphologic grounds alone, for the anatomic changes are nonspecific and may occur in a host of other conditions. Pertinent clinical aspects (for example, acute respiratory distress or sudden circulatory collapse within a few minutes following administration of the allergenic drug or agent) combined with pathologic findings such as pulmonary congestion or hemorrhage, acute pulmonary emphysema, or edema of the upper airways are features that characterize and substantiate anaphylactic reactions in man. The short interval between exposure and the systemic reaction to the offending agent appears as a critically important clinical feature in drug-induced anaphylactic reactions. Although in animal anaphylaxis there are particular target organs (which vary with different species), no single shock organ has been exclusively in-

volved in human cases. The clinicopathologic observations from our series of over 40 cases of fatal anaphylaxis provide support for the current view that the respiratory and cardiovascular systems may be the primary sites involved in such immediate hypersensitivity reactions. Future developments in histochemical and immunologic techniques may assist in providing a satisfactory explanation for the deaths of these patients.

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APPENDIX

Generic and Trade Names of Drugs

Sulfobromophthalein—Bromsulphalein
Lidocaine hydrochloride—Xylocaine
Sodium dehydrocholate—Decholin
Polymyxin B—Aerosporin
Tetracaine—Pontocaine
Acetrizoate sodium—Urokon
Sodium diatrizoate—Hypaque
Meglumine diatrizoate—Renografin

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